Bronchioloalveolar Carcinoma Presenting as Chronic Progressive Pulmonary Infiltrates in a Woman with HIV

A Diagnosis Worth Making

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Abstract: A 52-year-old woman with human immunodeficiency virus (HIV) developed weight loss, cough, and breathing difficulties, accompanied by extensive bilateral pulmonary infiltrates. A lengthy infectious disease and autoimmune workup failed to reveal the etiology or produce benefit. Expert pathology review raised the possibility of pure bronchioloalveolar carcinoma. The patient was treated with erlotinib and achieved a dramatic and prolonged response to treatment. After 14 months a solitary lung nodule developed which was excised. This demonstrated an invasive adenocarcinoma with an activating epidermal growth factor receptor mutation (exon 19 deletion). As this nodule had developed in the presence of erlotinib, this deletion is only presumed to reflect the initial driver of erlotinib sensitivity. Known acquired resistance mechanisms were explored, but the lesion was negative for both exon 20 T790M gatekeeper mutations and cMET gene copy number alterations. An as yet unknown mechanism of acquired resistance is therefore assumed to be involved in this case. We discuss the diagnosis and treatment of lung cancer in HIV-positive populations and review the general and specific characteristics of bronchioloalveolar carcinoma, including response to epidermal growth factor receptor inhibitors, and known mechanisms of acquired resistance. The predilection for lung cancer in HIV-positive patients, the diffuse nature of bronchioloalveolar carcinoma that can mimic infectious etiologies and the potential for dramatic responses to therapy make this an important diagnosis to consider in this setting.

Key Words: HIV, Human immunodeficiency virus, Bronchioloalveolar carcinoma, Bronchoalveolar carcinoma, BAC, Adenocarcinoma, Lung cancer, Lung carcinoma.

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A 52-year-old African American woman with human immunodeficiency virus (HIV) who was receiving highly active antiretroviral therapy (HAART) developed a chronic nonproductive cough accompanied by an interstitial infiltrate in the left upper lung field on chest radiograph.

The patient had previously been diagnosed with diabetes mellitus, controlled on two oral medications with no known systemic complications. In regards to her HIV infection, at presentation her CD4 count was 610 cells/ul; HIV RNA 4000 copies/ml. She had never been diagnosed with an opportunistic infection and her CD4 count usually ranged 500 to 600/ul. She had briefly smoked cigarettes but had quit more than 20 years ago (<1 pack year of exposure).

After presentation, an extensive pulmonary evaluation was performed over the next 22 months. Bronchoscopy was performed on five separate occasions and a video-assisted thoracoscopic surgery wedge biopsy of the right lower lobe. Cytology from multiple sputum samples and bronchial washings failed to reveal malignant cells. Bronchoscopic evaluation revealed copious serous secretions without evidence of any endobronchial lesion. Transbronchial biopsy specimens demonstrated nonspecific inflammation only. The wedge resection revealed acute bronchopneumonia, organizing pneumonia, and rare poorly formed granulomas.

More than 10 separate sputum and bronchial specimens were sent for acid fast bacilli stain and culture, fungal culture, aerobic and anaerobic bacterial culture, and viral cultures but no specific pathogens were identified. Extensive laboratory evaluations were performed for atypical causes of pneumonia without a clear etiology being found.

While these repeated evaluations were being performed, the patient continued to deteriorate clinically with progressive hypoxia, worsening of her pulmonary infiltrates and weight loss of more than 40 lbs. The patient was treated with multiple courses of antibiotics and empiric steroids without significant improvement in her pulmonary disease. *Cryptococcus neoformans* was cultured from a bronchial washing on one occasion and the patient was started on treatment with fluconazole and subsequently liposomal amphotericin B without clinical benefit.

Despite the previous bronchial washings and biopsies being reported as showing no evidence of malignant cells, review of these specimens at a multidisciplinary pulmonary

conference with expert lung cancer pathologists present raised the possibility that the patient's pulmonary disease could be due to bronchioloalveolar carcinoma (BAC). Subsequently, repeat bronchoscopy with multiple transbronchial biopsies of the left upper lobe revealed alveolar cells with histologic features consistent with pure BAC(Figure 1).

The patient was seen in consultation by medical oncology. Positron emission tomography/computed tomography (CT) imaging revealed extensive patchy infiltrates involving all lobes of both lungs as well as an area of more dense consolidation of the left upper lobe with an standard uptake value of 5.2 at its center. There was no evidence of extrathoracic spread or significant lymphadenopathy. The area of potential BAC on the last set of biopsies was considered too small to characterize further, and no additional molecular tests were conducted at that time. The patient was empirically started on an oral regimen of erlotinib 150 mg daily which was well tolerated and caused only a mild acneiform rash.

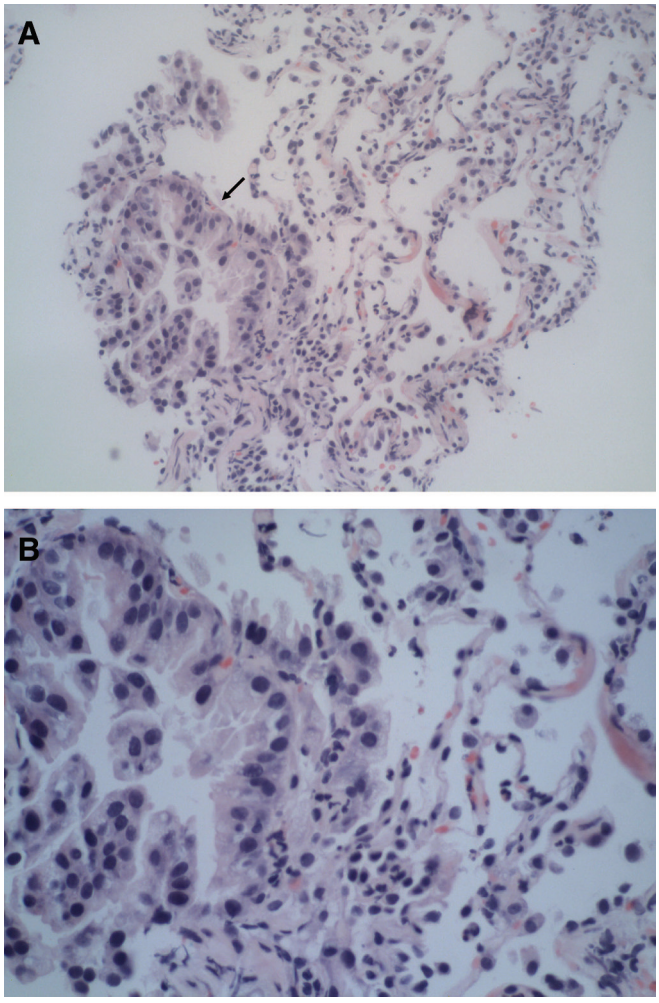

FIGURE 1. *A*, (H&E 200X) Bronchioloalveolar carcinoma within the transbronchial biopsy. Alveolar septa are lined by tall, columnar cells with mild nuclear pleomorphism and hyperchromasia, which project into spaces with papillary projections (arrow). The underlying lung architecture (right) is relatively preserved with thin vascular septa lined by benign pneumocytes. *B*, (H&E 400X) Bronchioloalveolar carcinoma within the transbronchial biopsy. The features of nuclear pleomorphism and hyperchromasia are better demonstrated on this high power view.

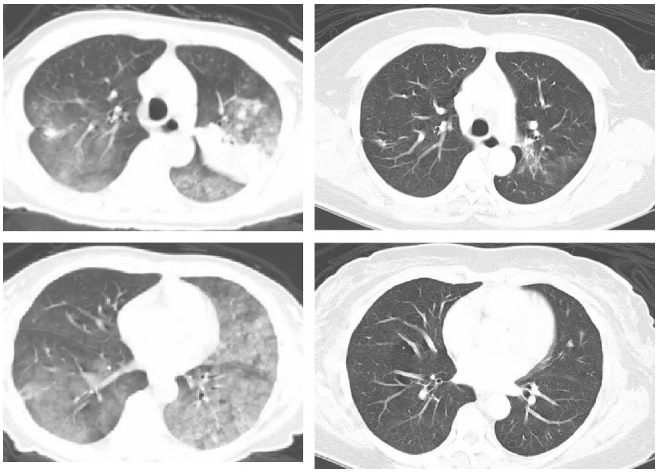

FIGURE 2. Near complete response to therapy with erlotinib. Computed tomography (CT) chest at initiation of treatment with erlotinib (left) and after 6 months of therapy with erlotinib (right).

After treatment for 3.5 months, a chest CT was repeated and demonstrated dramatic improvement with near resolution of pulmonary infiltrates (Figure 2). The patient clinically improved with resolution of cough and hypoxia along with a weight gain of 40 pounds. After 14 months of therapy with erlotinib, the patient developed a left lower lobe lung nodule that increased in size to 12 mm and was found to have a standard uptake value of 4.4 on positron emission tomography/CT. The suspicious lesion was excised through video-assisted thoracoscopic surgery wedge resection revealing a moderately differentiated adenocarcinoma which was EGFR positive by immunohistochemistry and demonstrated increased EGFR gene copy number by fluorescent in situ hybridization (FISH). Additional molecular correlates revealed that the tumor possessed an activating exon 19 deletion in EGFR (with wild type sequence in exons 20 and 21), was k-ras wild type, had no evidence of cMET gene copy number alteration by FISH, but did have increased Her2 gene copy number by FISH with modest Her2 expression (2+) by immunohistochemistry. The patient recovered quickly from the operation and continues on erlotinib.

DISCUSSION

Lung cancer remains an important differential consideration when investigating persistent pulmonary infiltrates in individuals infected with HIV. Several investigators have reported an increased incidence of lung cancer among HIV-positive populations in the HAART era.[1–3] Although some of this increased risk may be attributed to the higher prevalence of smoking, HIV has independently been associated with an increased risk of developing lung carcinoma and this risk seems to be unrelated to the level of HIV-induced immunosuppression.[4]

The combination of HIV infection and lung carcinoma generally portends a grim prognosis. Multiple small retrospective case studies have reviewed survival of HIV-positive patients compared with matched HIV-negative controls. The median survival of HIV-positive patients with lung cancer was approximately 4.5 months with 1 year survival of 10%. HIV-negative controls had a median survival of 10 months with 1 year survival of approximately 40%.[5] Hakimian et al.[6] recently performed a retrospective analysis of their experience treating 34 patients with HIV and lung cancer in the HAART era. Their experience supported previous survival findings and there seemed to be a trend towards worse survival among patients with CD4 counts <200. Unfortunately, randomized prospective studies have not been performed to assess the relative efficacy and toxicity of different chemotherapies in an HIV-positive population with lung cancer.

While there is little empiric data to guide chemotherapy for lung cancer in HIV infected patients, several investigators have studied the use of targeted EGFR inhibitors, such as erlotinib, in BAC. Since pure BAC is a relatively rare entity and it is difficult to rule out a small component of invasive adenocarcinoma, most clinical studies evaluating efficacy of treatment have included adenocarcinomas with any features of BAC. Although a subgroup analysis of Eastern Cooperative Oncology Group 1594 revealed a lower response rate to standard chemotherapy doublets in patients with BAC compared with other types of non-small cell lung cancer (6% versus 20%), there have not been any prospective randomized trials assessing the efficacy of different standard doublet chemotherapies in patients with BAC.[7] Nevertheless, there have been two trials which have specifically evaluated the efficacy of EGFR inhibitors in BAC. In Southwest Oncology Group 0126, gefitinib was evaluated in 90 patients with some histologic component of BAC and demonstrated a 19% response rate in chemo-naive patients and 9% in chemotherapy pretreated patients.[8] Some of these patients had complete responses. Similarly, erlotinib has been evaluated in a phase II study of 159 patients with advanced stage BAC lung carcinoma with overall response rate of 24% and an impressive 40% response rate in never smokers.[9] In this patient, on-treatment progression of a solitary nodule after 14 months of erlotinib prompted excision revealing an invasive adenocarcinoma with an activating EGFR mutation, EGFR gene amplification and Her2 gene amplification. Nevertheless, as all of these factors are normally associated with sensitivity to EGFR inhibition to varying degrees, the assumption is that this identifies the drivers present in the underlying BAC and responsible for the initial dramatic response, and that a secondary acquired resistance factor must also be present to drive the new BAC to adenocarcinoma progression.[10] In previous human studies, approximately 50% of cases of acquired resistance to EGFR inhibitors are due to the expression of the so-called gate-keeper T790M mutation in exon 20, however, this did not seem to be the case here.[10] Approximately 10 to 20% of cases of acquired resistance have recently been ascribed to cMET gene amplification, but again this did not seem to be the mechanism used in this case.[10]

As this case illustrates, the lepidic pattern of growth of BAC may produce extensive diffuse pulmonary infiltrates that can mimic those with infectious etiologies, delaying the diagnosis, particularly in those considered to be most at risk from infection. Selected patients with HIV and lung carcinoma can clearly have a dramatic response to modern anticancer therapies. Given the apparent increased risk of lung cancer in those with HIV, dedicated clinical trials of the tolerability and efficacy of different anticancer agents should be considered in this unique, but increasing, population. Information on whether the prevalence of known molecular drivers in non-small cell lung cancer differ significantly between those with and without HIV remains unknown.

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